Sexually Transmitted Diseases, Publish Ahead of Print
DOI: 10.1097/OLQ.0000000000000790

Defining the Urethritis Syndrome in Men Using Patient Reported Symptoms

Stephen J. Jordan[1], Kristal J. Aaron[1], Jane R. Schwebke[1], Barbara J. Van Der Pol[1], Edward W. Hook, III[1]

[1]Department of Medicine, University of Alabama at Birmingham School of Medicine, Birmingham, AL

Address correspondence to Stephen J. Jordan**:** Indiana University, 635 Barnhill Drive, Van Nuys Medical Science Bldg, MS 224E, Indianapolis, Indiana 46202. Phone: 1 (317) 274-8110. Fax: 1 (317) 274-1008. E-mail: jordansj@iu.edu.

Short Summary: 30 words (Max 30)

We evaluated the performance of seven self-reported symptoms in men with and without urethritis. Discharge and dysuria were associated with urethritis. Other symptoms, including urinary frequency and odor performed poorly.

To evaluate self-reported symptoms to guide urethritis diagnosis, symptomatic men being evaluated for urethritis were asked about seven symptoms captured during history-taking. Discharge and dysuria were significantly associated with urethritis and, when combined with genital irritation and itching, identified 95% of urethritis cases; odor and urinary frequency performed poorly.

This is the author's manuscript of the article published in final edited form as:

Jordan, S. J., Aaron, K. J., Schwebke, J. R., Van Der Pol, B. J., & Hook, E. W. I. (2018). Defining the Urethritis Syndrome in Men Using Patient Reported Symptoms. Sexually Transmitted Diseases, Publish Ahead of Print. https://doi.org/10.1097/OLQ.0000000000000790

Conflicts of Interest and Source of Funding:

S.J.J. has no conflicts of interest. K.J.A. has no conflicts of interest. J.R.S. has received honoraria, consulting fees, or research support from Cepheid, BD Diagnostics, LabCorp, and Hologic. B.V.D.P. has received honoraria, consulting fees, or research support from the following sponsors: Abbott Molecular Diagnostics, Atlas Genetics, BD Diagnostics, Beckman Coulter, Great Basin, Scientific, Cepheid, Hologic, Rheonix, and Roche Diagnostics. E.W.H. has received honoraria, research support, or consulting fees from Cepheid, BD Diagnostics, Gen-Probe Hologic, and Roche Diagnostics. Reagents and test kits for this study were supplied by Cepheid (Sunnyvale, CA). This work was funded from the National Institute of Allergy and Infectious Diseases of the National Institutes of Health Sexually Transmitted Infection Cooperative Research Center grant U19AI113212 (E.W.H., PI).

Key Words: Urethritis, Symptoms, Men

Urethritis is the most common genitourinary syndrome in sexually active men less than 50 years of age[1] with an estimated 2.8 million cases occurring annually in the United States.[2] Urethritis is associated with a number of etiological agents[3] including *Neisseria gonorrhoeae* (NG), *Chlamydia trachomatis* (CT), and *Mycoplasma genitalium* and causes a wide variety of symptoms, which include discharge, dysuria, localized pruritus, and penile tingling.[2, 4-7] To collect information on urethral symptoms, healthcare providers often use standardized data collection forms, driven by the rapid adoption of electronic medical records (EMR).[8] A result is that they may be both time consuming and inefficient as they encompass symptoms of both urinary tract infections (*e.g.* frequency, odor, *etc*) and sexually transmitted infections (*e.g.* discharge, dysuria, *etc*).[9] To our knowledge, there are no recent data on the relative importance of specific symptoms in predicting urethritis syndrome, which could help "re-calibrate" modern syndromic management approaches to urethritis. Given the increasing trend in sexually transmitted infection (STI) rates[10, 11] and utilization of healthcare resources,[12] such information could increase clinical efficiency by reducing unnecessary questioning and by shortening screening forms seeking urethritis symptoms. To this end, we evaluated 384 men attending a Birmingham, Alabama, STD Clinic and used data from the clinic's EMR and urethral Gram stain smears to diagnose symptomatic urethritis. Our primary objective was to test the performance of specific symptoms at accurately predicting urethritis. A secondary outcome was to compare our findings to an expert clinician-ranked survey of urethritis symptoms that predict urethritis in order to assess the accuracy of clinicians at predicting urethritis by syndromic management.

We enrolled 384 participants of whom 194 (51%) had at least one of the seven potential EMR urethritis symptoms (discharge, dysuria, urinary frequency, genital irritation, genital itching, genital lesions, and odor) captured on the EMR and were included in this study. All participants answered the same seven questions, none of which were specifically listed when

recruiting for the study. Participants were enrolled as part of a larger diagnostic study of non-gonococcal urethritis (NGU) in men ≥19 years of age, which included a detailed symptoms questionnaire and collection of a urethral swab for STI pathogen testing. All procedures were reviewed and approved by the local and NIH internal review processes and informed content was obtained for all men prior to enrollment. Men were 19 to 65 years old and 93% were black. Physical exams were performed by trained clinicians to determine the presence of urethral discharge and a urethral swab was obtained from all men for Gram stain testing of urethral secretions. Gram stains were read in blinded fashion by a single expert microscopist (JRS). 139 (64%) men were diagnosed with symptomatic urethritis based upon the presence of self-reported symptoms and either a discharge on physical exam (N = 106) or the presence of ≥5 polymorphonuclear cells per high-power field (PMNs/HPF) by microscopy of a Gram stain smear of urethral secretions (N = 124). Using nucleic acid amplification testing, 33 (17%) participants were positive for NG, 35 (18%) had positive tests for CT, and 19 (10%) had tests positive for both NG and CT. Then, we compared the results to a survey from 13 experienced sexual health clinicians, all leaders in the STI field, who were asked to rank the seven EMR symptoms in order of importance for predicting urethritis using a linear 1 (most important) to 7 (least important) scale.

As shown in Table 1, in the 194 symptomatic men, urethral discharge was the most common complaint (61%), followed by dysuria (50%), genital irritation and lesions (both 10%), then urinary frequency and genital itching (both 7%), and then odor (1%). 139 (72%) of the symptomatic men were subsequently diagnosed with documented urethritis. In men with symptomatic urethritis, discharge was the most common symptom (71%), followed by dysuria (59%). All other symptoms were present in ≤6% of men with urethritis. Stratified by GC urethritis or NGU, discharge was present in 88% of men with GC urethritis and 58% of men with

NGU. Dysuria was present in 75% of men with GC urethritis and 47% of men with NGU. The other symptoms were present in ≤9% of men with either GC urethritis or NGU (data not shown). Compared to men without urethritis, discharge or dysuria were significantly associated with a 2-fold increased risk for urethritis. In contrast, the other symptoms were independently either not associated with urethritis (frequency, itching or odor) or had an approximately 4-fold negative association with urethritis (lesions, irritation). We then used our study findings and the expert survey responses to determine the contribution of each symptom to accurate syndromic diagnosis of urethritis. All 13 surveyed expert clinicians identified either discharge (n = 9, 69%) or dysuria (n = 4, 31%) as the most important symptom predicting urethritis and all identified the other symptom (either dysuria or discharge) as the second most important (data not shown). The mean expert-ranked score and standard deviation for each symptom, from most to least important, were discharge (1.3 ± 0.48), dysuria (1.7 ± 0.48), urinary frequency (3.8 ± 1.14), genital irritation (4.1 ± 0.76), genital itching (mean 4.6 ± 1.12), genital lesions (5.9 ± 1.04), and odor (6.5 ± 0.78).

Given the strong association between dysuria or discharge and urethritis and our observation that almost half of men with symptomatic urethritis (n = 67, 48%) complained of more than one symptom (data not shown), we then calculated the proportion of documented urethritis diagnoses that could be identified by taking a step-wise combination approach to utility of urethritis symptoms. As shown in Table 2, the addition of self-reported dysuria to a discharge complaint captured an additional 22 (16%) of men with clinical urethritis diagnoses (87% total), compared with discharge alone. The addition of genital irritation added another 6 (4%) men, encompassing 91% of all urethritis diagnoses. The remaining 9% of all clinical diagnoses included the symptoms genital itching, genital lesions, and urinary frequency.

In this study, self-reported urethral discharge was the symptom most predictive of urethritis, present in 71% of men with clinical urethritis. Dysuria, the second most prevalent

symptom, was reported by 59% of men with urethritis. Only discharge and dysuria were significantly associated with a urethritis diagnosis and appear to increase the risk by 2-fold. Men with urethritis rarely complained of the remaining 5 symptoms, in which each occurred in ≤6% of men. In fact, only 4% (range 0–6%) of urethritis patients complained of frequency, genital irritation, itching, lesions or odor, which were either not associated with urethritis or were more likely to be associated with a diagnosis other than urethritis. This suggests that these symptoms provide specific information that, excluding discharge or dysuria, support an alternative diagnosis (*e.g.* lesions caused by HPV, etc.).

Our study suggests that discharge and dysuria are clearly the most important symptoms to ask men being evaluated for urethritis. The remaining symptoms of irritation, itching and lesions appear to be beneficial only when added to discharge and dysuria as, independently, they were not significantly associated with urethritis. Asking about urinary frequency or genital odor, in addition to the former symptoms, identified only two additional cases of urethritis suggesting there is little utility in adding those symptoms to either the clinical interview or in a symptom survey.

Genital irritation, genital itching, genital lesions, urinary frequency, and urinary odor were relatively infrequent, cumulatively comprising only 13% of urethritis diagnoses in differing proportions. This suggests that men may have difficulty articulating their symptoms perhaps colored by their pre-conceptions of what symptoms an STD "should" feel like. Specifically, men may have difficulty differentiating "genital irritation" from "genital itching" and combining them into a broader term may be appropriate. For example, in our study, four men admitted to irritation, but specifically identified their symptom as "tingling" (data not shown). As a simplifying strategy, we suggest the use of a broader, more encompassing term such as "genital discomfort" instead of "genital irritation" and/or "genital itching" which would identify 95% of

urethritis diagnoses, when combined with urethral discharge and dysuria. In contrast, adding urinary frequency or odor to the list of queried symptoms had little impact on the percent of identified urethritis cases (Table 2) and could likely be excluded from urethritis screening.

Our study has several limitations. In this single-center study, the majority of men in this study were African American, which is representative of our clinic population, and therefore these findings may not be generalizable to other populations. The GC rate was high in our study, and we cannot exclude that our findings may differ in populations with different STI rates and/or etiologies of urethritis (*e.g. M. genitalium, T. vaginalis, etc*), especially outside the U.S. We also used a Gram stain cutoff of ≥5 PMNs/HPF (recommended by the European NGU treatment guidelines)[13] in order to maximize the urethritis diagnosis specificity. It is possible that using the lower cutoff of ≥2 PMNs/HPF (recommended by the 2015 CDC STD treatment guidelines)[4] could have yielded different results. Although the latter cutoff appears to identify more chlamydia diagnoses,[13] whether it more accurately reflects urethritis remains unclear. Also, our study only enrolled men who presented to the STD clinic and we cannot rule out the possibility of a selection bias, given our study does not include men presenting to other clinics or mildly symptomatic men who did not come in for symptom evaluation.

In conclusion, in sexually active men who present with genitourinary complaints, a history of discharge and/or dysuria should prompt appropriate evaluation and screening for urethritis and could identify up to 87% of cases. If combined with discharge and/or dysuria, up to 95% of urethritis cases could be identified if genital irritation and/or itching was also present. Excluding discharge and dysuria, however, the other symptoms were not independently associated with a urethritis. Urinary frequency and odor were poor predictors of urethritis and can likely be excluded from symptom queries trying to identify men with symptomatic urethritis. These results could form the basis for an effective standardized EMR-based method for screening sexually-active men for symptomatic urethritis.

Acknowledgments:

The authors are grateful to Paula Dixon and Austin Culver for assistance with specimen processing/testing and Drs. Teri Anderson, Laura Bachmann, Dennis Fortenberry, William Geisler, Khalil Ghanem, H. Hunter Handsfield, David Martin, Angela Montgomery, Anne Rompalo, Bradley Stoner, Kimberly Workowski, and Jonathan Zenilman for their responses to the survey.

References

1. Bradshaw CS, Tabrizi SN, Read TRH, et al. Etiologies of Nongonococcal Urethritis: Bacteria, Viruses, and the Association with Orogenital Exposure. Journal of Infectious Diseases. 2006;193(3):336-45.
2. Brill JR**.** Diagnosis and treatment of urethritis in men. American family physician. 2010;81(7):873-8.
3. Martin D**.** Urethritis in Males. In: Holmes KK SP, Stamm WE, ed. Sexually Transmitted Diseases. 4th ed. New York: McGraw-Hill; 2008:1107-26.
4. Workowski KA, Bolan GA, Papp JR**.** Sexually transmitted diseases treatment guidelines, 2015.; 2015:1-137.
5. Bachmann LH, Manhart LE, Martin DH, et al. Advances in the Understanding and Treatment of Male Urethritis. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2015;61 Suppl 8:S763-9.
6. Shahmanesh M, Moi H, Lassau F, Janier M, Iusti/Who**.** 2009 European guideline on the management of male non-gonococcal urethritis. Int J STD AIDS. 2009;20(7):458-64.
7. Moi H, Blee K, Horner PJ**.** Management of non-gonococcal urethritis. BMC Infectious Diseases. 2015;15(1):294.
8. Jamoom E, Hing E**.** Progress with electronic health record adoption among emergency and outpatient departments: United States, 2006-2011; 2015.
9. Poissant L, Pereira J, Tamblyn R, Kawasumi Y**.** The impact of electronic health records on time efficiency of physicians and nurses: a systematic review. J Am Med Inform Assoc. 2005;12(5):505-16.
10. Organization WH**.** Global incidence and prevalence of selected curable sexually transmitted infections-2008. 2012.

11. Prevention CfDCa**.** Sexually Transmitted Disease Surveillance 2015. Atlanta: U.S. Department of Health and Human Services. 2016.

12. Statistics NCfH**.** Health, United States, 2016: With Chartbook on Long-term Trends in Health: Hyattsville, MD; 2017.

13. Rietmeijer CA, Mettenbrink CJ**.** Recalibrating the Gram Stain Diagnosis of Male Urethritis in the Era of Nucleic Acid Amplification Testing. Sexually transmitted diseases. 2012;39(1):18-20.

Table 1. Frequency of Symptoms Associated with Urethritis and Expert Clinicians' Valuation of the Urethritis Syndrome at Predicting Urethritis in Symptomatic Men

Urethritis Symptom	*% in Sx Men (n = 194)*	*% in Sx Men with Urethritis (n = 139)*	*% in Sx Men without Urethritis (n = 55)*	*Relative Risk (95% CI)*	*Expert Score[a] (Mean ± StDev)*
Discharge	61%	71%	36%	1.96 (1.36–2.82)	1.3 ± 0.48
Dysuria	50%	59%	27%	2.16 (1.37 – 3.40)	1.7 ± 0.48
Frequency	7%	6%	9%	0.63 (0.22 – 1.85)	3.8 ± 1.14
Irritation[b]	10%	6%	22%	0.26 (0.11 – 0.61)	4.1 ± 0.76
Itching	7%	5%	11%	0.45 (0.16 – 1.29)	4.6 ± 1.12
Lesions	10%	6%	20%	0.29 (0.12 – 0.68)	5.9 ± 1.04
Odor	1%	0%	2%	0.13 (0.0 – 3.22)	6.5 ± 0.78

Abbreviations: CI, confidence interval; Sx, symptomatic; StDev, standard deviation
[a]Score sorted from most important (1) to least important (7) by STD experts (*n* = 13).
[b]Genital irritation includes tingling and non-micturition-associated groin or penile pain.

Table 2. Percent of Clinical Urethritis Identified by One or More Symptoms (*n* = 139)

Symptom							*n* (%) Added	*n* (%) Total
Discharge							–	99 (71.2%)
Discharge	+ Dysuria						+ 22 (15.9%)	121 (87.1%)
Discharge	+ Dysuria	+Irritation					+ 6 (4.3%)	127 (91.4%)
Discharge	+ Dysuria	+Irritation	+ Itching				+ 5 (3.6%)	132 (95.0%)
Discharge	+ Dysuria	+Irritation	+ Itching	+ Lesions			+ 5 (3.6%)	137 (98.6%)
Discharge	+ Dysuria	+Irritation	+ Itching	+ Lesions	+ Frequency		+ 2 (1.4%)	139 (100%)
Discharge	+ Dysuria	+Irritation	+ Itching	+ Lesions	+ Frequency	+ Odor	+ 0	139 (100%)

Abbreviations: + indicates "and/or"